Epidemiology Pathophysiology and Management of Diabetes Mellitus Type 2

SHANKAR V. PANDHARE[1], BHIMASHANKAR S. HUCCHE[2], SHYAMLILA B. BAVAGE[3], NANDKISHOR B. BAVAGE[4]

[1] *B. Pharm Final Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[2] *Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[3] *Department of Pharmacognosy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[4] *Department of Pharmaceutical Chemistry, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

Abstract*— Globally, type 2 diabetes mellitus is a one of the most common diseases. Type 2 diabetes mellitus an is associated with the irreversible danger factors, for genetic, age, and ethnicity and reversible factors like physical activity, diet and smoking Type 2 diabetes mellitus is closely linked to the epidemic of obesity. people with Type 2 diabetes mellitus are at high risk for micro vascular complications [including nephropathy, retinopathy and neuropathy] and macro vascular complications [such as cardiovascular comorbidities] , due to hyperglycaemia and separate components of the insulin resistance syndrome. Environmental factors [e.g. physical inactivity, obesity and unhealthy diet] and hereditary variables add to the different pathophysiological unsettling influences that are liable for disabled glucose homeostasis in T2DM. Insulin resistance and impaired insulin secretion remain the deformities in T2DM, yet somewhere around six other pathophysiological irregularities add to the liberation of glucose digestion. The various pathogenesis aggravations present in T2DM dictate that multiple anti-diabetic agents, utilized in combination, will be needed to maintain norm glycaemia.

I. INTRODUCTION

Diabetes mellitus was first perceived as disease around 3000 years ago by the antiquated Egyptians and Indians, outlining some clinical feature basically the same as what we current know as diabetes. DM is a blend of two words, "diabetes" Greek word subordinate, implies siphon - to go through and the Latin word "mellitus" signifies sugary or sweet. In 1776, overabundance sugar in blood and urine was first affirmed in Great Britain. There are three type of diabetes mellitus type 1 [T1DM], diabetes mellitus type 2 and gestational DM [GDM]. [1]

There are three diabetogenic factors: environmental, polygenic, and the endogenous histological structural defects connected with the ADIA which interacts and contributes to the development and the progressive nature of Type 2 diabetes mellitus**.** Notwithstanding the contemporary generally acknowledged two trademark highlights of insulin obstruction and beta cell brokenness there is a tight relationship of T2DM with weight and stationary way of life. [2]

II. DEFINITION

Type 2 diabetes mellitus is a heterogeneous, multifactorial, polygenic disease characterized by a defect in insulin's secretion and action. [2]

The effect of cardiovascular disease on mortality and morbidity in people with diabetes has been known for years. About two-thirds of people with diabetes expire from cardiovascular disease [stroke, coronary heart disease, and other vascular diseases] **[**2]

Type 2 diabetes mellitus is categorized by deregulation of lipid, carbohydrate, and protein

digestion, and results from impaired insulin secretion and insulin resistance. Of the three major types of diabetes, T2DM is far more common than either type 1 diabetes mellitus [T1DM] or gestational diabetes. Over the past few years, our understanding of the turn of events and movement of T2DM has advanced quickly. It is a main cause is increasingly impaired insulin secretion by pancreatic β-cells, usually upon a background of pre-insulin resistance in skeletal muscle, liver and adipose tissue. Overt hyperglycaemia is preceded by prediabetes a high risk condition that predisposes people to type 2 diabetes mellitus development. Prediabetes is categorised by any one of the following: impaired fasting glucose [IFG] levels, impaired glucose tolerance [IGT]. Individual with IFG levels are arranged by fasting plasma glucose levels that are higher than ordinary however don't meet the models for the finish of diabetes. IGT is described by insulin obstruction in muscle and impeded late (second-stage) insulin discharge after a supper, while people with IFG levels show hepatic insulin opposition and debilitated early insulin emission. People with prediabetes have HbA1c levels between 5.7–6.4%; they address a heterogeneous gathering concerning pathophysiology and are clinically exceptionally assorted. Yearly change paces of prediabetes to type 2 diabetes mellitus range from 3% to 11% each year. [1]

III. EPIDEMIOLOGY

In 2007, type 2 diabetes represents a major public health issue all over the world, becoming a “diabetes epidemic” as stated by Zimmet. [3]

According to the reports by International Diabetes Federation (IDF), 387 million people have diabetes, which is expected to rise to 592 million by 2035**.** Statistical data suggest that the number of people with type-2 diabetes is increasing in every country, but the low and middle income countries are the most affected as they inhabit 77% of the total diabetic population**.** The situation is further worsened by the undiagnosed diabetes [fasting plasma glucose, >126 mg/dL] which affects approximately 179 million people worldwide**.** However, there lies a significant gap in the knowledge of diabetes and CVD epidemiology and associated risk factors among Indian population. [4]

Many developing nations such as India and China are presently experiencing rapid urbanization and economic development which has led to transition in nutrition patterns and sedentary lifestyle, and thus giving rise to cardio metabolic disorders. The Indian Diabetes Prevention Program (IDPP) suggests that after 3 years of follow-up, the relative risk reduction was reduced to 28.5% with life-style management, 26.4% with metformin, and 28.2% with the combined interventions compared with the control group. Urbanization reportedly causes significant reduction in physical activity with increase in body mass index (BMI) and upper body adiposity. [4]

Although a very high prevalence of type 2 diabetes has been observed in non-Caucasian groups [African Americans, Native Americans, Hispanics], type 2 diabetes occurs in all races. In the SEARCH study**,** the incidence rate (per 100,000 person-year) of type 2 diabetes among children and adolescents varies greatly by ethnicity, with the high estrates observed among youths aged 15–19 years in minority populations. In particular, the reported incidence rate was 49.4 for Native Americans, 22.7 for Asian/Pacific Islanders, 19.4 for African Americans, 17 for Hispanics, and 5.6 for non-Hispanic whites. [5]

In addition, cigarette smoking is a significant risk factor for developing T2DM, independent of body weight and other risk factors. Although genetics play an important part in the development of T2DM, the on-going diabetes epidemic cannot be explained by novel genetic mutations but is instead largely explained by the epidemic of obesity. Nevertheless, genes deter- mine how we respond to changes in the environment and vice versa. [1]

IV. PATHOPHYSIOLOGY

- β- Cell function

Type 2 diabetes is progressive, and one main factor responsible for this is a continued decline in β-cell function. Several studies have demonstrated that diabetes and prediabetes do not develop until the b-cell fails to compensate appropriately to the peripheral insulin resistance state. The ability of the b-cell to secrete sufficient insulin to adequately respond to the peripheral insulin resistance state depends on multiple factors, including b-cell mass and secretory capacity,

which are influenced by genetic and environmental factors. In fact, although the progressive loss of β-cell function could be due to different metabolic derangements (insulin resistance, lipotoxicity), several studies have suggested that β-cell dysfunction depends also on a pre-existing and perhaps genetically determined risk, which is crucial for β-cell dysfunction to occur. [5]

Insulin resistance is the earliest detectable abnormality in individuals who are likely to develop T2DM. However, overt T2DM does not occur unless β-cells are unable to secrete sufficient amounts of insulin to offset the insulin resistance. Multiple factors contribute to β-cell failure, including ageing, genetic abnormalities, in cretin hormone glucagon-like peptide 1 [GLP1] and gastric inhibitory polypeptide [GIP] resistance and or deficiency, lipotoxicity, glucotoxicity, insulin resistance leading to β-cell stress , hyper secretion of islet amyloid polypeptide [IAPP], reactive oxygen stress and activation of inflammatory pathways. [1]

To protect b-cell function, the most effective therapeutic strategy could be either to reduce the workload of β-cell or to let β-cell rest. These two targets could be achieved by change in lifestyle and or reducing the obesity, and ultimately the use of metformin. Lifestyle modification improves insulin sensitivity and hence reduces β-cell work load. In addition, insulin therapy has been shown to improve β-cell function probably through inducing β-cell rest. [4]

- Insulin secretion

β-cells integrate inputs from substrates [such as glucose, FFAs, arginine, fructose and amino acids], hormones and nerve endings to adjust insulin release in response to changing demands [for example, fasting–feeding cycles, exercise and stress] on a minuteto-minute basis in order to maintain normal blood glucose levels, and inter-individual differences affect this adjustment. For example, a lean, insulin-sensitive adult might need as little as 0.5U of insulin to dispose of an oral load of 75 g of glucose over 2 hours, whereas an obese, insulin-resistant, glucose-intolerant person might require 45U to perform the same task [~90-fold inter-individual difference]. In vivo tests in humans using intravenous or oral glucose, arginine, sulfonylureas (antidiabetic drugs) or mixed meals have demonstrated impaired β-cell function in overt T2DM. However, reliable quantitation of in vivo β-cell dysfunction requires some form of modelling. [1]

B-Cells are capable of sensing plasma glucose levels and releasing insulin. Rising plasma glucose levels enters the β-cells through the GLUT2 transporter and subsequently lead to a rise in the β-cell adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ratio. The rise in the ATP/ADP ratio initiates steps that lead to a depolarization of the cell membrane, an influx in calcium ions, and subsequent exocytotic release of insulin from storage granules. B-Cells attempt to maintain normoglycemia by modifying insulin secretion to affect the peripheral glucose disposal rates despite underlying IR. The ability to secrete adequate amounts of insulin depends on βcell function, β-cell insulin receptor interactions, and mass. [6]

The regulation of insulin secretion is complex. In addition to glucose, other nutrients [certain amino acids and free fatty acids, FFAs] stimulate insulin secretion. Gastric hormones, such as glucagon-like polypeptide-1 [GLP1] released at food intake, and cholinergic and β-2 adrenergic agonists may potentiate the glucose α2-adrenergic agonists, somatostatin and some prostaglandin inhibit insulin release. [8]

- Insulin resistance

Insulin resistance is a major feature of type-2 diabetes and develops in multiple organs, including skeletal muscle, liver, adipose tissue, and heart. The insulin receptor is a tyrosine kinase that is auto activated by promoting the tyrosine phosphorylation on itself and on downstream singling molecules such as insulin receptor substrate family members IRS-1 and IRS-2. The IRS proteins become phosphorylated on serine [and threonine] residues, probably by the action of multiple kinases. Several other molecules in the insulin singling pathway [e.g. m-TOR and phosphatidylinositol 3-kinase] transmit the activation signal downstream and also provide upstream negative feedback signals. [4]

Although the pathophysiological mechanism of type 2 diabetes is not completely understood, it is clear that insulin resistance plays an important role in its

development. Evidence of this comes from cross-sectional and longitudinal studies demonstrating that insulin resistance occurs 10–20 years before the onset of the disease and that it is the best predictor of whether or not an individual will later become diabetic. [5]

In addition, insulin resistance, by placing an increased demand on the b-cell to hyper secrete insulin, influences the progressive β-cell failure of type 2 diabetes. The precise mechanism(s) by which insulin resistance leads to β-cell failure remain(s) unknown, however a possible hypothesis is that the cause of insulin resistance is also directly responsible for the β-cell failure. [i.e,lipotoxicity] [5]

Obesity and physical inactivity lead to insulin resistance, which together with a genetic predisposition45, place stress on β-cells, leading to a failure of β-cell function and a progressive decline in insulin secretion. Insulin resistance precedes T2DM by many years. [1]

- The liver

The ability of insulin to suppress hepatic glucose production both in the fasting state and postprandially is normal in first degree relatives of type 2 diabetic patients. It is the increase in the rate of postprandial glucose production that heralds the evolution of IGT. Eventually, both fasting and postprandial glucose production increase as type 2 diabetes progresses. Hepatic insulin resistance is characterized by a marked decrease in glucokinase activity and a catalytic increased conversion of substrates to glucose despite the presence of insulin. Thus, the liver in type 2 diabetes is programmed to both overproduce and underuse glucose. The elevated free fatty acid levels found in type 2 diabetes may also play a role in increased hepatic glucose production. In addition, recent evidence suggests an important role for the kidney in glucose production via gluconeogenesis, which is unrestrained in the presence of type 2 diabetes. [7]

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Metformin

It is the only biguanide available. It is currently the recommended first line treatment and the most widely used insulin sensitizer in the elderly because of effectiveness in lowering blood glucose, a low risk of hypoglycemia and relatively low adverse effect profile. It can be used as monotherapy or in combination with other oral hypoglycemic agents such as sulfonylurea, GLP-1 receptor agonists, and DPP-4 inhibitors or with insulin. Together with diet, metformin can reduce fasting glucose by 50–70 mg/dL and the HbA1c from 1.3 to 2.0%. It lowers blood glucose levels by sensitizing the liver to the effects of insulin. [9]

Sulfonylureas

Sulfonylureas have been used to treat type 2 diabetes since 1942 and require functional pancreatic b-cells for their hypoglycemic effect. All currently available sulfonylureas bind to specific receptors on b-cells, resulting in closure of potassium ATP channels. As a result, calcium channels open, leading to an increase in cytoplastic calcium that stimulates insulin release. [7]

Thiazolidienediones

Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in peripheral tissue especially in muscle and also decrease hepatic gluconeogenesis by activating the peroxisome proliferator-activated receptor gamma. [9] Thiazolidinediones activate PPARc (peroxisome proliferator-activated receptor gamma), resulting in stimulation of adipogenesis and suppression of osteoblastogenesis. [10]

Meglitinide

Meglitinides are insulin secretagogues with rapid onset and relatively short duration of action that control postprandial hyperglycemia. Hypoglycemia risk is less than with sulfonylureas, which makes this class of medication a more suitable alternative in elderly patients with CKD or those that are intolerant to metformin or sulfonylureas. Nateglinide is mainly metabolized by the liver and excreted by the kidneys unchanged. Repaglinide is metabolized primarily (90%) by the liver and the remaining 10% is metabolized by the kidneys, requiring dosage adjustment in renal failure. [9]

α-Glucosidase inhibitor

Members of this class act by slowing the absorption of carbohydrates from the intestines and thereby minimize the postprandial rise in blood glucose . Gastrointestinal side-effects require gradual dosage increments over weeks to months after therapy is initiated. Serious adverse reactions are rare, and weight gain may be minimized with this therapy. Acarbose, the agent of this class in clinical,use may be added to most other available therapies. [7]

Insulin

The first available insulin analog is lispro insulin, representing a two-amino acid modification of regular human insulin. Lispro insulin does not form aggregates when injected sc, allowing it to have a more rapid onset and a shorter duration of action than regular insulin. [7] Insulin is the most effective antidiabetic medication when dosed appropriately. The progressive decline of β-cell function with advancing age means that the majority of elderly diabetics will require insulin eventually. Major limitations include inability to self-administer due to poor vision, impaired manual dexterity, poor functioning or impaired cognition and potential for hypoglycaemia. [9]

REFERENCES

[1] Ralph A. DeFronzo, Ele Ferrannini, Leif Groop, Robert R. Henry, William H. Herman, Jens Juul Holst, Frank B. Hu, C. Ronald Kahn, Itamar Raz, Gerald I. Shulman, Donald C. Simonson, Marcia A. Testa and Ram Weiss, Type 2 Diabetes Mellitus.

[2] Melvin R Hayden, Islet Amyloid, Metabolic Syndrome, and the Natural Progressive History of Type 2 Diabetes Mellitus, Page No: 128

[3] M. Virallya , J.-F. Blickléb , J. Girardc , S. Halimid , D. Simone,f,g, P.-J. Guillausseaua, Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutically perspectives.

[4] Ankita Pandey, Sheetal Chawla, Prasenjit Guchhait, Type-2 Diabetes: Current Understanding and Future Perspectives , Page No: 507

[5] EBE D'ADAMO, MD, SONIA CAPRIO, MD, Type 2 Diabetes in Youth: Epidemiology and Pathophysiology, Page No: S161.

[6] Prasanth N. Surampudi, MD, Jennifer John-Kalarickal, MD, and Vivian A. Fonseca, MD MRCP, Emerging Concepts in The Pathophysiology of Type 2 Diabetes Mellitus. Page No: 219.

[7] RICHARD J. MAHLER AND MICHAEL L. ADLER, Type 2 Diabetes Mellitus: Update on Diagnosis, Pathophysiology, and Treatment.

[8] C. G. OÈ STENSON, The pathophysiology of type 2 diabetes mellitus: an overview. Page No: 242-243.

[9] Anees A Siddiqui*, Shadab A Siddiqui, Suhail Ahmad, Seemi Siddiqui, Iftikhar Ahsan, Kapendra Sahu, Diabetes: Mechanism, Pathophysiology and Management-A Review, Page No: 10

[10] J. Compston, Type 2 diabetes mellitus and bone, Page No: 142